DOCKET NO.: ISIS-3105 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: #33

Teng and Hardee

Serial No : **09/108,673** Group Art Unit: **1636**

Filed: **July 1, 1998** Examiner: **W. Sandals**

For: **COMPOSITIONS AND METHODS FOR THE DELIVERY OF OLIGONUCLEOTIDES VIA THE ALIMENTARY CANAL**

Assistant Commissioner for Patents
Washington, D C 20231

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

I, Ching-Leou C. Teng, Ph D., do hereby declare as follows:

1 I am currently an Assistant Director of Drug Delivery Research and Pharmaceutical Development at Isis Pharmaceuticals, Inc. ("Isis") in Carlsbad, California. My responsibilities include the following: conducting preformulation and formulation for new oligonucleotide drugs; performing formulation research to improve existing formulations or alter the route of administration; designing and conducting validation studies and published technique reports for the chemistry, manufacturing, and controls (CMC) and microbiology sections of new drug applications (NDA); participating in the preparation of the CMC section for investigational new drug (IND) and NDA submissions; coordinating the drug product fill in-house and contract manufacturer for pre-clinical and clinical studies; and animal model development for penetration enhancer screening and formulation evaluation of oligonucleotide via oral administration. I have a Ph D. in pharmaceutics and have worked in this field for more than 25 years. My *curriculum vitae* is attached hereto as Exhibit A.

2. From 1992 to 1998, I was a Senior Scientist in drug Discovery Research and Pharmaceutical Development at Isis, where my responsibilities were also as listed above.

3. From 1988 to 1992, I was a Reviewer in the Pharmacokinetics Evaluation Branch, Division of Pharmaceutics, Food and Drug Administration (FDA), Rockville, Maryland.

4. From 1986 to 1988, I was a Postdoctoral Research Fellow in the college of Pharmacy at the University of Michigan. My research focused on the development of a reactor to remove heparin in extracorporeal circulation.

5. From 1981 to 1986, I was a graduate student in the College of Pharmaceutics at the University of Michigan. I received my Ph D. in 1986, and my dissertation was entitled "Kinetics of adhesion of polymer-coated particles to intestinal mucous surfaces"

6. From 1978 to 1981, I was a Chemist in the Pharmacokinetic Drug analysis Laboratory, Veterans Administration Hospital, Fargo, North Dakota. I obtained my Master's degree in Pharmaceutical Science from North Dakota State University.

7. From 1974 to 1978, I was a Registered Pharmacist, Pharmacy Department, Mackay Memorial Hospital, Taipei, Taiwan. I received my Bachelor of Science degree in 1974 from Taipei Medical College

8. I am a co-inventor of the above-referenced patent application along with Greg Hardee.

9. *In situ* perfusion studies were performed using the sodium salts of caprylic (C8) and lauric (C12) acid essentially as described in Example 4 of the specification of the above-referenced application, except that rat jejunum was used instead of rat ileum. Six rats were administered C8 only (1% w/v), three were administered C12 only (1% w/v), and three were administered a combination of C8 and C12 (0.5% each, w/v) The average individual absorptions

for C8 and C12 were 0.9%, and 8.3%, respectively. The combination of C8 and C12, however, resulted in an absorption of 11%. This combination of C8 and C12 produced a result greater than would have been expected in view of the individual absorptions obtained.

10 I declare that all statements made herein are of my own knowledge true and statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Ching-Leou Teng

Ching-Leou C. Teng, Ph D

Jan 18, 2002

Date

EXHIBIT A

Ching-Leou C. Teng, Ph.D.

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ACADEMIC SUMMARY:

1986-1988 Postdoctoral Research Fellow.
College of Pharmacy, The University of Michigan
Research focused on the development of a reactor to remove heparin in extracoporeal circulation. Advisor, Dr. Victor Yang.

1981-1986 Ph.D. in Pharmaceutics.
College of Pharmacy, The university of Michigan.
Dissertation: Kinetics of adhesion of polymer-coated particles to intestinal mucous surface. Advisor, Dr. Norman F. H. Ho.

1978-1981 M.S. in Pharmaceutical Science.
College of Pharmacy, North Dakota State University.
Thesis: I: Cd/Sephadex interaction
II: Cd biological uptake
Advisor, Dr. Fred F. Farris.

1970-1974 B.S. in Pharmacy.
Taipei Medical College, Taiwan.

EXPERIENCES:

March 1992-Present: ISIS Pharmaceuticals, Carlsbad, CA

April 1998 Assistant Director, DDR&PD
March 1992 Senior Scientist, Drug Delivery Research and Pharmaceutical Development (DDR&PD)

1. Conducted preformulation and formulation studies for new drug entities
   - Intraocular injection – carried out from pre-clinical to market
   - Intravenous injection – phase III
   - Enema – phase II
   - Solid formulation – pre-clinical
2. Performed formulation research to improve the existing formulation or alter the administration route
   - Controlled release formulation for subcutaneous injection
   - Transdermal drug delivery
   - Microemulsion for oral delivery
2. Designed and conducted validation studies and published technique reports for the CMC and microbiology sections of NDA
3. Participated in the preparation of CMC section for IND and NDA submissions
4. Coordinated the drug product fill in house and contract manufacturer for pre-clinical and clinical studies
5. Animal model development for enhancer screening and formulation evaluation of oligonucleotide via oral administration

1988-1992: Food and Drug Administration, Rockville, Maryland
Reviewer, Pharmacokinetics Evaluation Branch, Division of Biopharmaceutics,

1. Reviewed IND and NDA submissions of cardio-renal and gastrointestinal drug products and recommended the approval of the biopharmaceutic section to the New Drug Evaluation Divisions.
2. Designed and evaluated protocols for pharmacokinetics, bioequivalence and dose proportionality studies
3. Consulted Pharmaceutical industries regarding scientific and regulatory issues.
4. Advised medical officers, pharmacologists and chemists on scientific and regulatory issues concerning new drug applications.
5. Represented the Division of Biopharmaceutics in the preparation of stereoisomer guidelines.
6. Conducted mathematic modeling to understand the pharmacokinetic of enterohepatic circulation drugs (ursodeoxycholic acid)

1978-1981: Veterans Administration Hospital, Fargo, North Dakota
Chemist, Pharmacokinetic Drug Analysis Laboratory

1974-1978: Mackay Memorial Hospital, Taipei, Taiwan
Registered Pharmacist, Pharmacy Department,

PUBLICATIONS:

1. S. M. Johnson, C. Chan, S. Cheng, J. L. Shimek, G. Nygard, and S. K. Wahba Khalil, "Isocratic High-Performance Liquid Chromatographic Method for the Determination of tricyclic Antidepressants and Metabolites in Plasma" J. Pharm. Sci., 71, 1027, (1982).

1. C. L. C. Teng and N. F. H. Ho, "Mechanistic Studies in the Simultaneous Flow and adsorption of Polymer-Coated Latex Particles on Intestinal Mucus I: Methods and Physical Development "J. Controlled Release, 6, 133, (1987).

2. Ching-Leou C. Teng, Jae-Seung Kim, Friedrich K. Port, Thomas W. Wakefield, Gerd O. Till, and Victor C. Yang, "a Protamine Filter For Extracorporeal Blood Heparin Removal" American Society of Artificial and Internal Organs Transactions, 34, 743-746 (1988).

3. Victor C. Yang and Ching-Leou Teng, "A Protein-Bound Polymeric Filter Device for Extracorporeal Blood Deheparinization" Polymeric Materials Science and Engineering, 58, 116-119 (1988).

4. Ching-Leou C. Teng and Victor C. Yang, "A Facile Colormetric Protamine Titration Method" J. of Laboratory and Clinical Medicine, 43, 498-504, (1989).

5. Jae-Seung Kim, Christopher Vincent, Ching-Leou C. Teng, Thomas W. Wakefield, and Victor C. Yang, "A Novel Approach to Anticoagulation Control" American Society for Artificial Internal Organs Transactions, 35, 644-646, (1989).

6. You-Yin Fu, Ching-Leou C. Teng, and Victor C. Yang, "Rapid and Precise Whole Blood Protamine Titration" American Society of Artificial and Internal Organs Transactions, 36, M660-663, (1990).

7. Victor C. Yang and Ching-Leou C. Teng, "An Immobilized Protamine System for Removing Heparin in Extracorporeal Blood Circulation' Biomimetic Polymers, Plenum Press, 175-190 (1990).

8. Victor C. Yang, Ching-Leou C. Teng, and Jae-Seung Kim, "A Filter for the Prevention of both Heparin and Protamine Induced Complications Associate with Extracorporeal Therapy" Biomedical Instrumentation and Technology, 24, 433-439 (1990).

9. Victor C. Young, Friedrich K. Port, Ching-Leou C. Teng, Jae-Seung Kim, Gerd O. Till, and Thomas W. Wakefield, "The use of Immobilized Protamine in Removing Heparin and Preventing Protamine Induced Complexes During the Extracorporeal Blood Circulation" Anesthesiology, 75:288-297 (1991).

10. Victor C. Yang, You-Yin Fu, and Ching-Leou C. Teng, "A Method for the Quantitation of Protamine in Blood" Thrombosis Research , 74, 427-434 (1994).

11. Bennett, F.C, Butler, M., Cook, P.D., Geary, R., Levin, A., Mehta, R., Teng, C-L., Deshmukh, H.M., Tillman, L. and Hardee, G.E. Antisense oligonucleotides based therapeutics. In:Templeton, N.S and Lasic, D.D, eds. Gene Therapy. Marcel Dekker, Inc. 2000:305-332.

12. S. Kevin Li, Abdel-Halim Ghanem, Ching-Leou Teng, Gregory E. Hardee, and William I. Higuchi, "Iontophoretic Transport of Oligonucleotide Across Human Epidermal Membrane:a study of the NERNST-PLANCK model" J. Pharm. Sci. 90, 915-931 (2001)

13. WeiQi Lin, Michel Cormier, Ahmad Samiee, Angie Griffin, Bonny Johnson, Ching-leou Teng, Gregory E Hardee, and Peter E Daddona, "Transdermal Delivery of Antisense Oligonucleotide with Macroflux Microprojection Patch Technology" Pharm. Res. In Print

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1. Teng, Ching-Leou; Cook, Philip D.; Tillman, Lloyd; Hardee, Gregory E.; Ecker, David J.; Manoharan, Muthiah. Compositions and methods for non-parenteral delivery of oligonucleotides. Application: WO 9960012 A1 19991125.

2. Teng, Ching-Leou; Hardee, Greg. Compositions and methods for the oral delivery of antisense oligonucleotide via alimentary canal. Application: WO 9901579 A1 19990114.

3. Hardee, Gregory E.; Tillman. Lloyd G.; Mehta, Rahul C.; Teng. Ching-Leou. Multiparticulate formulations containing polycationic complexes. Application: WO 0050050 A1 20000831